

IN THE CLAIMS:

Please cancel claims 2, 6, 10, 11, 12, 13, 14, 22, 23, 24, 25, 26, 27, 28, 29, 30, 33, 34, 35, 39, 40, 41, 42, 44 and 46.

1. (Original) An isolated nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunit, comprising a sequence of nucleotides encoding a T-type calcium channel  $\alpha_{1I-1}$  subunit selected from the group consisting of:

(a) a sequence of nucleotides that encodes a human T-type calcium channel  $\alpha_{1I-1}$  subunit and comprises the sequence of nucleotides set forth in one of SEQ ID NO.:18;

(b) a sequence of nucleotides having at least 95% sequence identity or is exactly complementary to the nucleotide sequence set forth in SEQ ID NO.:18,

(c) a nucleotide sequence varying from the nucleotide sequence specified in (a) or (b) as a result of degeneracy of the genetic code;

(d) biologically active fragments of (a), (b), or (c), that encodes polypeptide capable of forming a functional T-type calcium channel.

2. Canceled

3. (Original) A substantially pure polypeptide comprising an amino acid sequence encoded by the nucleotide sequence as set forth in one of SEQ ID NOS.:18 or 20.

4. (Original) A substantially pure polypeptide comprising an amino acid sequence as set forth in one of SEQ ID NOS.:19 or 21.

5. (Original) A substantially pure polypeptide which has at least 80 % identity to the amino acid sequence of SEQ ID NO.:19, which may include up to  $N_a$  amino acid alterations over the entire length of SEQ ID NO.:19, wherein  $N_a$  is the maximum number of amino acid alterations, and is calculated by the formula

$$N_a = X_a - (X_a Y),$$

in which  $X_a$  is the total number of amino acids in SEQ ID NO.:19, and Y has a value of 0.80, wherein any non-integer product of  $X_a$  and Y is rounded down to the nearest integer prior to subtracting such product from  $X_a$ .

6. Canceled

7. (Original) An expression vector comprising the nucleic acid molecule of claim 1 operably linked to a regulatory nucleotide sequence that controls expression of the nucleic acid molecule in a suitable host cell.

8. (Amended) A recombinant host cell transfected by the expression vector of claim [8] 7.

9. (Original) The cell of claim 8 which is also transformed with DNA expression vectors encoding additional calcium channel subunits necessary and sufficient for assembly of a functional voltage-gated calcium channel.

10. Canceled

11. Canceled

12. Canceled

13. Canceled

14. Canceled

15. (Original) An isolated nucleic acid molecule of an alternative splicing variant of a human T-type calcium channel subunit, comprising a sequence of nucleotides encoding a T-type calcium channel  $\alpha 1I$ -2 subunit selected from the group consisting of:

(a) a sequence of nucleotides that encodes a human T-type calcium channel  $\alpha 1I$ -1 subunit and comprises the sequence of nucleotides set forth in one of SEQ ID NO.:20;

(b) a sequence of nucleotides having at least 95% sequence identity or is exactly complementary to the nucleotide sequence set forth in SEQ ID NO.:20,

(c) a nucleotide sequence varying from the nucleotide sequence specified in (a) or (b) as a result of degeneracy of the genetic code;

(d) biologically active fragments of (a), (b), or (c), that encodes polypeptide capable of forming a functional T-type calcium channel.

16. (Amended) A method for identifying candidate compounds capable of binding to the ~~variant product~~ polypeptide of claim 3 and modulating its activity the method

comprising: (i) contacting a candidate compound with the substantially pure polypeptide of claim 3; and (ii) determining the effect of said candidate compound on the biological activity of said protein or polypeptide and selecting those compounds which show a significant effect on said biological activity.

17. (Original) A method according to claim 16, wherein the compound is an agonist and the measured effect is increase in the biological activity.

18. (Original) A method according to claim 17, wherein the compound is an antagonist and the effect is decrease in the biological activity.

19. (Original) A method for detecting an  $\alpha_1\text{I}$  isoform in a first biological sample, comprising the steps of: (a) contacting a detectable probe with said biological sample suspected of containing said variant under conditions favoring the formation of a complex between said probe and any said variant; and (b) detecting said complex wherein the presence of said complex correlates with the presence of the desired amino acid in said biological sample.

20. (Original) The method according to claim 19, wherein said probe is an antibody.

21. (Original) The method according to claim 19, wherein said probe is an immunologically active polypeptide specific for said isoform.

22. Canceled

23. Canceled

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30. Canceled

31. (Original) A method for treating a subject having a stroke, epileptic seizure, or traumatic brain injury comprising administering to a subject in need of such treatment an inhibitor of the human T-type calcium channel  $\alpha_{1I-1}$  subunit polypeptide in an amount effective to inhibit voltage regulated calcium influx.

32. (Amended) The method of claim ~~32~~ 31, wherein the inhibitor is selected from the group consisting of an antibody which selectively binds the human T-type calcium channel  $\alpha_{1I-1}$  subunit polypeptide, an antisense nucleic acid which binds a nucleic acid encoding human T-type calcium channel  $\alpha_{1I-1}$  or an  $\alpha_{1I-2}$  subunit polypeptide and a dominant negative human T-type calcium channel  $\alpha_{1I-1}$  or an  $\alpha_{1I-2}$  subunit polypeptide.

33. Canceled

34. Canceled

35. Canceled

36. (Original) A method for identifying lead compounds for a pharmacological agent useful in the treatment of disease associated with increased or decreased voltage regulated calcium influx mediated by a human T-type calcium channel comprising:

(i) providing a cell expressing a human T-type calcium channel isoform subunit polypeptide designated herein as  $\alpha_{1I-1}$  or  $\alpha_{1I-2}$ ;

(ii) contacting the cell with a candidate pharmacological agent under conditions which, in the absence of the candidate pharmacological agent, to thereby cause a first amount of voltage regulated calcium influx into the cell; and

(iii) determining a test amount of voltage regulated calcium influx as a measure of the effect of the lead compounds for a pharmacological agent on the voltage regulated calcium influx mediated by a human T-type calcium channel, wherein (a) the test amount of voltage regulated calcium influx which is less than the first amount indicates that the

candidate pharmacological agent is a lead compound for a pharmacological agent which reduces voltage regulated calcium influx and (b) wherein a test amount of voltage regulated calcium influx which is greater than the first amount indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which increases voltage regulated calcium influx.

37. (Original) The method of claim 36, further comprising loading said cell with a calcium-sensitive dye which is detectable in the presence of calcium, wherein the calcium-sensitive dye is detected as a measure of the voltage regulated calcium influx.

38. (Original) A method for identifying compounds which selectively bind a human T-type calcium channel  $\alpha_{1I-1}$  subunit isoform comprising, (i) providing a test cell preparation, wherein said cell expresses a human T-type calcium channel  $\alpha_{1I-1}$  subunit isoform, (ii) providing a control cell preparation, wherein said cell expresses a human T-type calcium channel non- $\alpha_{1I-1}$  subunit isoform, with the proviso that the cell in the cell preparation is identical to the test cell except for the expression of a non- $\alpha_{1I-1}$  isoform being expressed, (iii) contacting the test cell preparation and the control cell preparation with a compound, and (iv) determining the binding of the compound to the test cell preparation and the control cell preparation, wherein a compound which binds the test cell preparation but does not bind the control cell preparation is a compound which selectively binds the human T-type calcium channel  $\alpha_{1I-1}$  subunit isoform.

39. Canceled

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41. Canceled

42. Canceled

43. (Original) An isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of:

- (a) an amino acid sequence of SEQ ID NOS.:19 or 21,
- (b) a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NOS.:18 or 20, wherein said naturally-occurring amino acid

sequence has the ability to regulate voltage gated calcium influx under physiological conditions and

- (c) an immunogenic fragment derived from one of SEQ ID NO.:19 or 21.

44. Canceled

45. (Amended) A recombinant human cell line which has been engineered to express a heterologous protein, the cell line comprising at least one host cell transformed or transfected with a heterologous nucleic acid molecule of ~~one of claim 1 or 15~~ that expressed an  $\alpha 1I$  isoform polypeptide.

46. Canceled

47. (Amended) A method of producing the recombinant protein according to claim 3 ~~or~~ 4, comprising:

- (a) inserting the nucleic acid sequence as set forth in one of SEQ ID NO.:~~18~~ 19 or 21 or a fragment or variant thereof into an expression vector;
- (b) transferring the expression vector into a host cell; or transfecting or transforming a host cell with the expression vector of step (a) above;
- (c) culturing the host organism under conditions appropriate for amplification of the vector and expression of the protein; and
- (d) harvesting the recombinant protein from the culture.

48. (Original) A method for identifying compounds that modulate the activity of T-type calcium channel  $\alpha 1I$  subunit, the method comprising:

comparing the difference in the amount of transcription of a reporter gene in a cell in the presence of the compound with the amount of transcription in the absence of the compound, or with the amount of transcription in the absence of a heterologous T-type calcium channel  $\alpha 1I$  subunit , whereby compounds that modulate the activity of the heterologous calcium channel subunit in the cell are identified, wherein the cell comprises a nucleic acid molecule that encodes a reporter gene construct containing a reporter gene in operative linkage with one or more transcription control elements that is regulated by a calcium channel and furthermore the cell is a eukaryotic cell transfected with a nucleic acid molecule comprising the coding portion of the sequence of nucleotides set forth in one of SEQ ID NO.: 18 or 20.

49. (Original) A method for identifying a test compound capable of modulating the activity of T-type calcium channel  $\alpha_1I$  subunit, the method comprising:

(i) suspending a eukaryotic cell in a solution containing the compound and a calcium channel selective ion;

(ii) depolarizing the cell membrane of the cell, and

(iii) detecting the current or ions flowing into the cell,

wherein the eukaryotic cell comprises a functional calcium channel that contains at least one subunit encoded by a heterologous nucleic acid comprising the coding portion of the sequence of nucleotides set forth in SEQ ID NOS.: 18 or 20, and

wherein the current that is detected is different from that produced by depolarizing the same or a substantially identical cell in the presence of the same calcium channel selective ion but in the absence of the test compound.

50. (Original) The method of claim 49, wherein prior to the depolarization step the cell is maintained at a holding potential which substantially inactivates calcium channels that are endogenous to the cell.